ultraviolet light in the wards themselves and similar measures seem to us to be too clumsy and elaborate for general adoption, particularly under conditions of modern warfare. The expense of some of these measures must also be considerable. There is, moreover, no guarantee that under stress they might not break down. For these reasons, segregation of all infected cases appears to us to be simpler and more likely to be of value. Its only drawback is that it appears administratively to be difficult, but this is not a valid objection.

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JAUNDICE AS A PÆDIATRICIAN SEES IT*

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THERE is ample reason for inquiring into a symptom such as jaundice, even though the variety of conditions in which it may occur ranges widely in the clinical field. The closer we can approach to a clear understanding of its physiological and biochemical derivation, the greater becomes its value as a diagnostic and prognostic index. The pædiatrician finds a particular interest in weighing the changing significance of any symptom, jaundice included, at different age levels. Moreover, re-appraisal is called for from time to time by reason of the fact that from decade to decade there is apt to be a shift in the incidence of many of the diseases with which jaundice is associated.

The colouring of the skin and other tissues in icterus reflects their staining with bilirubin which has spilled over, so to speak, from abnormally high levels in the blood. Presumably there is an element of selective adsorption involved here, for jaundice may be clearly present when plasma filtrates like cerebrospinal fluid and tears remain colourless. It is stated that in adults jaundice becomes clinically apparent when the serum bilirubin level exceeds a value of about 2 mg. per 100 c.c., some variation in the threshold level being an individual characteristic. In children, however, the threshold level is appreciably higher, and in the neonatal period jaundice may not be detectable until the serum-bilirubin concentration has passed the 5 mg. mark, or in some infants even 12 mg.[1] Physicochemical reasons for this age-factor in tissue adsorption of bilirubin are not apparent. Indeed, the phenomenon seems paradoxical, in that one might have expected that the thinness and relative transparency of an infant's tissues would allow one to detect icterus with relatively small increments in the blood bilirubin level.

Jaundice, in any event, depends on an abnormally high level of bilirubinæmia, and before going on to consider its clinical significance we ought to look back for a moment at the factors which allow bile pigment to accumulate in the blood. Hæmolysis of red cells is constantly going on as a physiological process, the liberated hæmoglobin being converted into bilirubin by the reticulo-endothelial cells, especially by those of the bone marrow. Bilirubin is also being constantly excreted, and is passed from the blood in liver sinusoids through their endothelial

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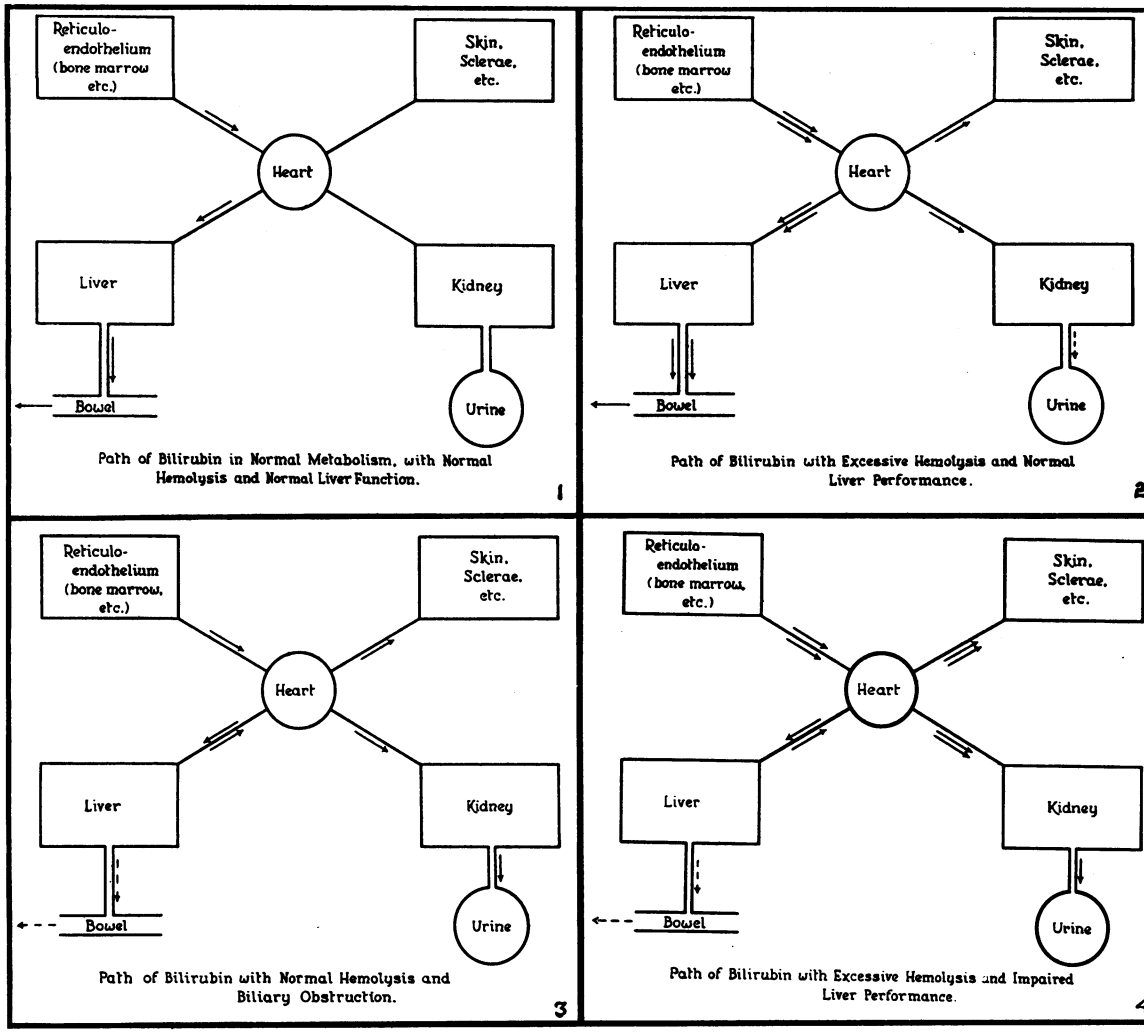

lining into the polygonal hepatic cells and on out into the bile capillaries which form the tributaries of the bile-duct system. Elevation of the blood bilirubin concentration can result from excessive hæmolysis, from interference with the process of excretion in the liver, or from combinations of these two. We must look, therefore, for causes of jaundice in processes which lead to an abnormally rapid rate of erythrocyte destruction and in disturbances of that special function of the liver which has to do with clearing the blood of this particular breakdown product of hæmoglobin. The bilirubin excreting power of normal liver tissue is considerable. It does not seem to be greatly impaired by physical pressure, for the extent to which metastatic neoplasms may invade the liver without causing icterus is well known. There are certain diseases which seriously compromise some of the other functions of the liver without appreciably affecting bilirubin excretion; an example is glycogen storage disease, which selectively interferes with normal hepatic glycogenolysis. On the other hand, anoxæmia, circulatory failure, or almost any infection may compromise the liver's capacity to excrete bilirubin, and certain conditions such as infectious hepatitis seem to produce a selective disturbance of bilirubin clearance and are commonly accompanied by jaundice.

Not all of the bilirubin encountered in the blood in different clinical states behaves alike with respect to its ability to escape from the blood stream by penetration of the limiting endothelial membrane. When jaundice depends on biliary obstruction or on injury to hepatic cells bile pigment is promptly and readily detectable in the urine. On the other hand, in jaundice dependent chiefly on excessive hæmolysis, as in familial hæmolytic icterus (often called acholuric jaundice), the urine may fail to give a positive test for bile pigment. In both of these types of jaundice the pigment is identical and its concentrations in the blood may be at equal levels. The differences in its behaviour

depend on physico-chemical influences. These factors again are poorly understood, but we may approach them with some measure of confidence because certain relatively simple tests exist which enable us to distinguish diffusible bilirubin from non-diffusible bilirubin, and help in the differential diagnosis of the physiological disturbances underlying jaundice in a given case. I refer first to the van den Bergh test, which in its simplest qualitative or semi-quantitative form consists of the mere addition of Ehrlich's diazo reagent to a sample of the serum under investigation. If the mixture takes on a purplish colour at once, the presence of an appreciable quantity of diffusible bilirubin is revealed. This is also referred to as a "direct" reaction. If the purple colour develops only on standing for some minutes, non-diffusible or "indirect" reacting bile pigment is present in amounts greater than normal, for the reagent is of such limited sensitivity that little if any change in colour is developed by mixing it with normal serum. The addition of alcohol brings out all the colour that can be developed by both the diffusible and the non-diffusible fractions present in the sample, and serves as a measure of the total level of bile pigment, a device which is especially useful in cases where both excessive hæmolysis and impaired liver performance are present. Another very simple test is carried out by precipitating the serum or plasma proteins by the addition of acetone in excess and filtering or centrifuging the precipitate. A yellow colour visible in the precipitate indicates diffusible or direct bilirubin.

These simple tests are of great value in differential diagnosis of the underlying causes of jaundice in any given case, by reason of the well established fact that the presence in the blood serum of appreciable quantities of direct or diffusible bilirubin carries with it an immediate indictment of the liver, or at least of the mechanism involved in the delivery of bile into the intestinal lumen. The block may be at any level from the papilla of Vater on up through the biliary duct system to the hepatic cells themselves; but at least this degree of organ localization is possible. Although inspection of the stools and chemical testing for bile pigment when the stools are pale or chalky should not be neglected, a positive direct van den Bergh test in a sample of blood serum is of greater value in that it is less likely to give false or equivocal information. Stools may be clay-coloured after the feeding of protein milk and yet may contain bilirubin; or they may be of normal or nearly normal colour when injury to the liver cells is incomplete or when the bile duct system is only partially blocked, or even with complete biliary obstruction when enough bile pigment diffuses into the intestinal lumen at other levels of the alimentary tract. This last phenomenon has often been observed even in anatomically proved cases of complete obliteration of the bile-duct system. And again, though the urine should always be tested for bile pigment in cases of jaundice, it is not always accurate to infer that the presence of bilirubinuria indicates major liver dysfunction. For the active intravascular hæmolysis which results from a mismatched transfusion is accompanied by an abundance of bile pigment in the urine so soon after the catastrophe as to make it unlikely that liver damage plays a part.

In cases of obvious jaundice, then, in addition to the usual clinical observations which in the course of time afford a measure of the severity and course of jaundice as a symptom, it is pertinent to follow the red cell count and hæmoglobin level as indexes of significant blood destruction, to note the colour of the stools and, where necessary, to test them for bile pigment, to look for bilirubin in the urine by any one of the simple chemical tests or even by the foam test, to perform the van den Bergh test or the acetone precipitation test on a sample of serum, and, if adequate technical facilities are at hand, to measure from time to time the total bilirubin concentration in the serum or plasma. In pædiatric work these rather simple manœuvres can be counted on with confidence to furnish all the data one will need for evaluating the factors involved in pathogenesis, and thus for arriving at a reasonably accurate diagnosis of the underlying disease process. Moreover, the results of such tests furnish us the most useful of all bases of classification of clinical causes of jaundice, a classification, moreover, which is founded on objective information and which does not lose its bearings in a fog of assumptions. The evaluation of the cause of jaundice in adults may require the application of a wider variety of diagnostic tests, such as the determination of serum phosphatase concentration[2] and Hanger's cephalin flocculation test;[3] but I shall not attempt to discuss these, inasmuch as they have not been found essential in working with infants and children.

In the past few years my associates at the Babies' Hospital and the Sloane Hospital for Women in New York have been paying particular attention to jaundice occurring in the neonatal period. The contributions of Canadian investigators in this field have been monumental, and a large fraction of our own work has served merely to corroborate the data already obtained and the interpretations already applied, notably by the Montreal group.[4] Students of the problem now generally concede that in any large group of newborn infants about one-third to one-half will show clinically manifest jaundice; that this jaundice appears oftenest on the second or third day, increases in intensity for a few days (usually only one or two) and then fades out more slowly; that in general its severity matches closely the elevation of the bilirubin concentration in the infant's blood serum; and that, as a rule, the earlier jaundice appears, the more intense is it apt to become and the longer may it be expected to endure.

It is agreed that virtually all newborn infants show a hyperbilirubinæmia during the first week of life, whether they develop clinical jaundice or not; that the source of this extra bilirubin in the average case is the superabundance of erythrocytes which, though they were necessary for tissue oxidation at the relatively low oxygen pressures of the intrauterine fetal circulation, are no longer essential to the infant who depends on his lungs rather than on his umbilical cord for his oxygen supply; an explanation long ago made clear by Goldbloom and his collaborators.[5] It is becoming increasingly evident, however, that the piling up of large amounts of bilirubin in the blood of these infants and their tendency to exhibit jaundice is not exclusively dependent on the amount of blood which they get rid of in this adjustment, for other factors come into play. The one about which controversy has been longest indeterminate pertains to the adequacy of liver function at this age. Evidence arrived at in various ways now seems to bring a clear indictment against the liver. This organ may at such times be only immature; it is certainly not permanently disabled; but in even the mildest of these cases of neonatal jaundice the levels of bilirubinæmia attained seem to depend in part on some factor other than hæmolysis and new formation of bilirubin, and that factor is inferred to be liver insufficiency. In the moderately severe and in the severe cases the argument for liver damage is incontrovertible.

Another significant feature on which attention has recently been focused anew is the demonstration that the hæmolytic process and the piling up of bile pigment in the blood commences before birth and therefore cannot depend exclusively on the adjustment to the oxygen pressure of respired air. Although practically all infants are born with a higher level of bilirubin in their umbilical cord blood than could be considered normal for an adult, the infants with the highest levels are precisely the ones who later go on to develop neonatal jaundice. Nearly twenty years ago Williamson[6] had demonstrated the occurrence and suggested the importance of this intra-uterine hæmolytic process by showing that the infants who developed neonatal jaundice were the ones in whose placentas the largest deposits of iron had accumulated, and this iron was rightly presumed to represent the residuum of hæmoglobin breakdown. Recent studies carried out by immunologists[7] indicate that under certain conditions the mother may develop agglutinins and hæmolysins to the blood of her offspring while it is still unborn, and that even before birth some of these antibodies may pass the placental barrier, enter the fetal circulation, and there initiate intravascular hæmolysis. These observations, while still incomplete and of preliminary scope, provide a working hypothesis to explain the familial occurrence of icterus gravis and erythroblastosis fœtalis in a more satisfactory manner than any other theory of pathogenesis that has thus far been brought forward. Whether this theory of sensitization, so to speak, of the mother to the erythrocytes of her child *in utero* may be extended to account for milder instances of neonatal jaundice, for the frequency with which jaundice is encountered among premature infants, and for other related peculiarities of neonatal behaviour in regard to bilirubin metabolism, remains to be worked out.

In differential diagnosis of causes of jaundice during the first week after birth the rule, obviously, is to regard all cases as examples of physiological neonatal jaundice until proved otherwise. We now recognize a smooth, progressive gradation of cases of jaundice caused by this mechanism from the simplest, most transitory, example through all degrees of

severity up to the rapidly fatal cases with intense jaundice, known in the older terminology as icterus gravis. But sometimes the cases of only slightly less severity survive; indeed, they may develop an even more intense jaundice than some of the fatal cases which end in death before there has been time to pile up the greatest possible store of bilirubin in the tissues. It is becoming customary in some centres of study to call these survivors examples of erythroblastosis fœtalis, or erythroblastosis neonatorum, even when their blood stream fails to contain an excess of erythroblasts. A better device possibly would be to refer to them all as examples of hæmolytic dyscrasia of the newborn, putting the emphasis on the underlying pathogenesis of the symptom rather than on an accidental morphological accompaniment of only a fraction of the total number of cases, and admitting from the start that all grades of severity may be encountered.

The important diagnostic and prognostic features which have emerged from recent studies are that the severe cases can often be recognized because of the early development of jaundice, discoloration of the amniotic fluid and of the vernix caseosa bearing witness to the onset of active hæmolysis even before birth; that in the severe and serious cases there is a rapid intensification of jaundice for as many as five and even six days after birth; that for a time increasing amounts of bile will be detectable in the patient's urine, while at the same time the van den Bergh reaction in the blood serum, originally mainly "indirect", soon comes to show a strong direct reaction, indicating that the excretory function of the liver has been overwhelmed and that intrahepatic bilirubin has piled up in amounts large enough to cause actual obstruction and rupture of bile canaliculi; and that the infants who survive are prone to have a large, hard liver for several weeks. A certain proportion of them, fortunately not over 10 per cent, will eventually show serious retardation of mental and behaviour development, although these last most ominous manifestations may not be apparent until many months after the jaundice has entirely disappeared.

During the stage of rapid hæmolysis which accompanies the active phase of the disease process these patients may quickly become desperately anæmic. Since anoxia of liver cells is one of the factors which is known to add to the liver's inability to excrete bilirubin through the normal channels one might hope to retard this process by early resort to transfusion, but we have time and again seen transfusion serve only to feed fuel to the flames, permitting further hæmolysis to take place and adding to the burden of bilirubin thrown against the already overtaxed liver. The work of Levine and his collaborators[7] on blood agglutinins has furnished at least a partial explanation of this phenomenon, and has led to the general warning that neither parent should be used as a donor under these circumstances. Selection of a blood relative of the mother as a donor offers a favourable probability of avoiding further hæmolysis of the transfused cells by the infant's plasma.

After the first week or ten days of post-natal life a continuing increase in the severity of jaundice usually points in another direction, and tends to incriminate the excretion process in the liver or to arouse suspicion of obstruction of the bile ducts themselves. This is particularly true of cases which have begun in a mild way, in contrast to those just described in which jaundice was apparent at birth or on the first day of life. In all infants at this age (that is, during the second and third weeks of life) active hæmolysis is still going on, for the process of adjustment to the arterial oxygen saturation of pulmonary respiration has not yet been completed, and it is the rule for the hæmoglobin curve to be still falling; but, even so, even with this extra burden of bilirubin to deal with the infant's liver should by this time have adapted itself to its task. With increasing jaundice at this age one will almost always find that the serum gives a strong direct van den Bergh reaction, and not infrequently the liver can be observed to be enlarging progressively.

Jaundice developing or increasing perceptibly during the second week of life used to focus attention on three principal diagnostic possibilities, neonatal sepsis, syphilis, and congenital malformation of the bile passages, with the last of the three being regarded as the least likely on the basis of pure probability. However, times seem to have changed—at least, in New York. Neonatal sepsis is, for one thing, definitely more rare than was formerly the case, and when we do encounter it, jaundice does not appear to play as large a part in its symptomatology as was once taught. Can it be that the syndrome which in another day was called "birth sepsis with jaundice" may have had a different pathogenesis? Icterus gravis had been

known to obstetricians for more than fifty years, but, traditionally, it was uniformly fatal; recovery wasn't "cricket".

Erythroblastosis fœtalis and the non-fatal cases of icterus gravis or of the hæmolytic dyscrasia of the newborn have been under active discussion for little more than a decade. It seems quite possible, on reflection, that cases of jaundice which nowadays would be put in one of these latter categories might, fifteen, twenty, or twenty-five years ago, have been blamed (as was so much else, to be sure) on birth sepsis. Times have changed too with regard to congenital syphilis, so that teaching hospitals experience more and more difficulty in finding enough clinical material for educational purposes, and we have to go far back in our records for a case of syphilitic jaundice in an infant.

And so the tortoise has caught up with both of these hares, and congenital malformation of the bile ducts with obstruction has now come to be in our experience the commonest cause of progressively increasing jaundice of early infancy. It is important to emphasize the characterization, "progressively increasing". We do not expect that these patients will give a history of having been jaundiced at birth.[8] In fact, many times nothing unusual is noticed until the patient is a week or ten days old, and even at that time the degree of jaundice may not be intense. We do not even expect the parents to notice anything wrong with the child's stools or urine, and in the majority of instances their inquiry as to the cause of the jaundice bespeaks curiosity rather than alarm. By the time the patient is brought for study he may have failed to gain in weight and vigour at the average rate and may show minor digestive symptoms such as anorexia and regurgitation, or even occasional vomiting, but these are signs devoid of specific significance. We do expect to find that in addition to readily visible jaundice he has enlargement and increased firmness of the liver, and his spleen is apt to be easily palpable. Unlike the patients with severe degrees of neonatal jaundice of hæmolytic origin, who seldom if ever exhibit either itching of the skin or a tendency to hæmorrhage, the infants with jaundice due to congenital malformation of the bile ducts are prone to show one or both of these signs. Some of them are constantly restless and uncomfortable and keep pawing at their trunks and buttocks, which may be covered with scratch marks. About one-third or more of them bleed with unusual ease, sometimes from known trauma, sometimes apparently spontaneously. Their blood-clotting time is often prolonged, and a deficiency of prothrombin can be demonstrated by appropriate analysis. A diagnosis of congenital malformation of the bile passages, suspected on clinical evidence alone, can usually be confirmed by additional laboratory tests, such as have already been described.

Every effort should be made to identify these cases early and to explore them surgically in the hope that some procedure for establishing an effective channel between liver and gut will be applicable. Only by such means can one expect to arrest the course of a relentlessly progressive and eventually fatal biliary cirrhosis. In this respect our experience at the Babies' Hospital has been less fortunate than that reported by some others; too often the anomaly found at exploratory operation is such that no remedial procedure is feasible. It is a matter of luck, and of luck alone, whether the point of obstruction lies above or below the junction of the cystic duct with the common bile duct. In the former case no anastomotic operation is feasible; in the latter, cholecystoduodenostomy or cholecystgastrostomy can at least be attempted. Probably the largest series of successful operations in congenital obstruction of the bile ducts reported in the literature is that described by Ladd, of Boston.[9] In 1935 he was able to cite 9 effective operations out of a total of 15 attempted.

While congenital malformation of the bile passages now accounts for the majority of cases of jaundice in which this sign commences around the second week of life, or is seen to increase in severity at that age, it does not monopolize the field. However, it is difficult to generalize about other types because of the fact that they are prone to differ widely and to represent a great variety of causal elements. We have seen obstructive jaundice caused by compression of the common bile duct by a hæmatoma in the wall of the duodenum, by dilatation of the gut above a congenital duodenal membrane, by tuberculous lymph nodes, and by swollen leukæmic nodes. Still another patient with obstructive jaundice was found to be suffering from a rare protozoan disease, toxoplasmosis, which in other cases has affected the brain and meninges and the retina, but which in this case apparently

involved the liver as well. There have been still other cases which not only fulfilled the usual criteria for the diagnosis of congenital biliary atresia but which at operation were found to have a collapsed gall bladder containing only colourless mucoid material and thin, cord-like and apparently completely atretic bile ducts; yet, after a hopeless prognosis had been given, some of these patients (we have seen two, and other clinics have had comparable experiences) have gone on to complete recovery with disappearance of jaundice, recession of the swollen liver, and reappearance of bile in the stools in normal amounts. Adequate explanation of such fortunate reversals of expectation is impossible, but it is clear that in dealing with cases of jaundice developing in early infancy but after the age at which physiological icterus is to be expected one must be prepared for surprises.

From the age of a few months to about six years there comes a lull during which jaundice as a symptom is relatively rare. When present it is more apt to depend on excessive hæmolysis as the predominating factor, and the resulting anæmia, whether it be of acute or of chronic type, is likely to dominate the symptomatology. Without entering at length into a listing or discussion of the various types of anæmia which may be involved in this respect, it may be pointed out that, taken by and large, an increasing proportion of the cases encountered have their origin in an unfavourable response to sulfanilamide or to one of the related drugs. Although hæmolytic crises of this sort may be dramatic, attended with fever, hæmoglobinuria, some degree of vasomotor collapse, and with all of the manifestations of a rapidly progressing anæmia, including even air-hunger, they are usually survived if the cause is promptly recognized and further administration of the drug stopped. Jaundice may appear within the first few hours of the attack, or not until the following day. The van den Bergh reaction of the serum, at first indirect only, later usually changes in part at least to direct. There is reason to believe that these acute hæmolytic reactions to sulfanilamide are more commonly encountered in children than in adults.[10]

From the age of about six years on up to puberty jaundice increases again in frequency, and the variety of its clinical causes broadens out. At this age level children begin to be more susceptible to the mildly communicable disease, infectious hepatitis or acute catarrhal jaundice; the number of cases of rheumatic carditis increases, and there is greater likelihood of jaundice related to cardiac failure; furthermore, examples of jaundice accompanying pneumonia or appendicitis become more numerous. In cases in which the symptom icterus dominates the total clinical picture, infectious hepatitis will rightly be the first possibility to be considered. This is one of the outstanding examples of obstructive jaundice. Of the etiology of this disease little is yet known; persistent failure to demonstrate a specific bacterial etiology perhaps justifies the inference that a filterable virus is concerned. While it tends to be a troublesome rather than a serious disease, one occasionally encounters cases in which the course is both severe and prolonged and in which permanent damage to the liver leads to cirrhosis. The true etiology in such instances is not open to objective proof, in the absence both of specific cultural or immunological procedures and of pathognomonic morphological changes verifiable by biopsy; yet the association of these cases with epidemics lends strong probability to this interpretation. It is to be hoped that progress will be made in this field so that the accuracy of diagnosis may become comparable to that which characterizes the identification of another and rarer form of infectious jaundice, Weil's disease, or leptospirosis icterohæmorrhagica.

In this cursory survey of some of the conditions which produce the clinical symptom jaundice, much has necessarily been omitted and much has been touched on so briefly as possibly to obscure, rather than clarify, the underlying considerations of etiology and pathogenesis. I have tried to hold to the goal of viewing clinical syndromes from the standpoint of their physiological substrate and to keep in mind, as the pædiatrician must always do, the changing incidence of disease with changing age; and speaking only as a pædiatrician, but recognizing at the same time that a few stray shots may have ricocheted off into the adjacent domain of the internist, I have endeavoured to outline in a general way the program of further inquiry which should come to mind when one is confronted with a patient who is jaundiced.

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THE TREATMENT OF HYDRONEPHROSIS SECONDARY TO ABERRANT RENAL VESSELS*

BY F. S. PATCH AND J. T. CODNERE†

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VASCULAR anomalies of the kidney and the harmful effects which they produce at times, present important problems in diagnosis and treatment. While modern methods of urological investigation have solved many of the diagnostic difficulties, in the field of treatment there is still a lack of unanimity in urological methods dealing with the hydronephrosis, which results from the obstructive action of renal aberrant vessels.

Accessory renal vessels were found in 21 per cent of 1,237 kidneys examined post mortem. Because of the intimate relation between lower polar aberrant vessels and the ureter, it is fortunate that only 6 per cent are of this variety. Except for occasional difficulties experienced at operation, if they are not recognized, upper polar vessels are relatively unimportant. It is also fortunate that lower polar vessels do not always obstruct the ureter, and produce hydronephrosis and its concomitant complications.

The rôle played by the aberrant vessel crossing in front of the ureter or behind it, has occasioned much argument among urologists. Some believe the vessel to be the primary factor in the production of hydronephrosis, while others are as firmly convinced that the hydronephrosis results from a renal ptosis, which causes the ureter to sag across the vessels. A variant of this view was advanced by Winsbury-White, that "the compression of the ureter by the blood vessel is but a complication of a pre-existing hydronephrosis".

Quinby has suggested that in its earlier stages, the hydronephrosis is produced from the irritation of the pulsation of the aberrant artery, which disrupts or inhibits peristalsis, thereby inducing urinary stasis. Geraghty and Frontz, for reasons which do not seem very convincing, concluded that the hydronephrosis in this, as in several other conditions, is due to an inflammatory contraction of the uretero-pelvic junction.

That a vessel without the intervention of any other factor may produce serious obstruction is shown by an autopsy finding, which I am enabled to report, through the kindness of Dr. R. R. Struthers, at that time head of the Department of Pædiatrics of the hospital.

A small infant, 1 month old, was admitted to the Pædiatric Service, with a history of pyuria from its birth. The infant died soon after admission from what was considered a bilateral obstructive uropathy. Autopsy revealed a bilateral hydronephrosis, and hydroureter, beginning immediately above vascular obstructions caused by the passage of both ureters under the external iliac arteries. The obvious character of the obstructive process resulting from this intimate contact of vessel and ureter seemed to offer an unanswerable argument on behalf of those who claim that the aberrant

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